```
=> d his

     (FILE 'HOME' ENTERED AT 18:40:02 ON 03 FEB 2003)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 18:40:14 ON 03 FEB
     2003
L1        17145 S VIRUS AND LIGAND
L2          453 S (MIX? OR MIXTURE)(8A)L1
L3        25253 S (MIX? OR MIXTURE)(8A)(VIRUS OR LIGAND)
L4           87 S L1 AND L3
L5           59 DUP REM L4 (28 DUPLICATES REMOVED)
L6         6006 S NON-COVALENT
L7         9012 S NON-COVALENT?
L8           38 S L1 AND L7
L9           22 DUP REM L8 (16 DUPLICATES REMOVED)

=> d bib ab 1-22 l9

L9   ANSWER 1 OF 22  CAPLUS  COPYRIGHT 2003 ACS
AN   2003:53545  CAPLUS
TI   Oil bodies and associated proteins as affinity matrices
IN   Moloney, Maurice; Boothe, Joseph; Van Rooijen, Gijs
PA   Sembiosys Genetics Inc., Can.
SO   U.S., 47 pp., Cont.-in-part of U.S. 5,856,452.
     CODEN: USXXAM
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.         KIND  DATE            APPLICATION NO.  DATE
     ---------------    ----  --------        ---------------  --------
PI   US 6509453          B1   20030121        US 1999-319275   19990827
     US 5856452          A    19990105        US 1996-767026   19961216
     WO 9827115          A1   19980625        WO 1997-CA951    19971205
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR,
             KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
             US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
             GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
             GN, ML, MR, NE, SN, TD, TG
PRAI US 1996-767026     A2   19961216
     WO 1997-CA951      W    19971205
AB   The invention concerns a method for the sepn. of a target mol. from a
     mixt.  The method employs oil bodies and their assocd. proteins as
     affinity matrixes for the selective, non-covalent
     binding of desired target mols.  The oil body proteins may be genetically
     fused to a ligand having specificity for the desired target mol.
     Native oil body proteins can also be used in conjunction with an oil body
     protein specific ligand such as an antibody or an oil body
     binding protein.  The method allows the sepn. and recovery of the desired
     target mols. due to the difference in densities between oil bodies and aq.
     solns.
RE.CNT  15    THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9   ANSWER 2 OF 22  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:595119  CAPLUS
DN   137:137272
TI   Designs of labels for detection with a surface-selective nonlinear optical
     technique
IN   Salafsky, Joshua S.
PA   USA
```

SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002061415	A1	20020808	WO 2001-US22412	20010717

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-265755P P 20010201
AB The invention concerns second harmonic, sum and difference frequency generation and their use to detect a variety of processes, which are otherwise undetectable, using nonlinear-active labels. The labels must have as high a hyperpolarizability as possible. Several designs for large hyperpolarizability second-harmonic active labels are described herein. These labels can be attached to any target mol. or particle, resulting in more highly nonlinear-optically active targets.
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 22 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 2003:12195 SCISEARCH
GA The Genuine Article (R) Number: 625ZL
TI Integrin alpha 8 beta 1 mediates adhesion to LAP-TGF beta 1
AU Lu M; Munger J S; Steadele M; Busald C; Tellier M; Schnapp L M (Reprint)
CS CUNY Mt Sinai Sch Med, Dept Med, New York, NY 10029 USA (Reprint); NYU, Sch Med, Dept Med, New York, NY 10016 USA; NYU, Sch Med, Dept Cell Biol, New York, NY 10016 USA; Univ Washington, Harborview Med Ctr, Seattle, WA 98104 USA
CYA USA
SO JOURNAL OF CELL SCIENCE, (1 DEC 2002) Vol. 115, No. 23, pp. 4641-4648. Publisher: COMPANY OF BIOLOGISTS LTD, BIDDER BUILDING CAMBRIDGE COMMERCIAL PARK COWLEY RD, CAMBRIDGE CB4 4DL, CAMBS, ENGLAND.
ISSN: 0021-9533.
DT Article; Journal
LA English
REC Reference Count: 26
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The development of fibrosis is a common response to a variety of injuries and results in the net accumulation of matrix proteins and impairment of normal organ function. We previously reported that the integrin alpha8beta1 is expressed by alveolar interstitial cells in normal lung and is upregulated during the development of fibrosis. TGFbeta1 is an important mediator of the inflammatory response in pulmonary fibrosis. TGFbeta1 is secreted as a latent protein that is **non-covalently** associated with latency-associated peptide (LAP) and requires activation to exert its effects. LAP-TGFbeta1 and LAP-TGFbeta3 contain the tripeptide sequence, arginine-glycine-aspartic acid (RGD), a known integrin recognition motif. The integrin alpha8beta1 binds to several **ligands** such as fibronectin and vitronectin through the RGD sequence. Recent reports demonstrate that the integrins alphavbeta1, alphavbeta6 and alphavbeta8 adhere to LAP-TGFbeta1 through the RGD site. Therefore, we asked whether LAP-TGFbeta1 might be a **ligand** for alpha8beta1 and whether this may be important in the development of fibrosis. We found that cell lines transfected with alpha8 subunit were able to spread on and adhere to recombinant LAP-TGFbeta1 significantly

better than mock transfected cell lines. alpha8-transfected cells were also able to adhere to LAP-TGFbeta3 significantly better than mock transfected cells. Adhesion to LAP-TGFbeta1 was enhanced by activation of alpha8beta1 by Mn2+, or 8A2, an integrin beta1 activating antibody. Furthermore, cell adhesion was abolished when we used a recombinant LAP-TGFbeta1 protein in which the RGD site was mutated to RGE. alpha8beta1 binding to LAP-TGFbeta1 increased cell proliferation and phosphorylation of FAK and ERK, but did not activate of TGFbeta1. These data strongly suggest that LAP-TGFbeta1 is a **ligand** of alpha8beta1 and interaction of alpha8beta1 with LAP-TGFbeta1 may influence cell behavior.

L9 ANSWER 4 OF 22 MEDLINE DUPLICATE 1
AN 2002235723 MEDLINE
DN 21969902 PubMed ID: 11972774
TI C-terminal domains of Listeria monocytogenes bacteriophage murein hydrolases determine specific recognition and high-affinity binding to bacterial cell wall carbohydrates.
AU Loessner Martin J; Kramer Karl; Ebel Frank; Scherer Siegfried
CS Institut fur Mikrobiologie, FML Weihenstephan, Technische Universitat Munchen, Weihenstephaner Berg 3, D-85350 Freising, Germany.. M.J.Loessner@Lrz.tum.de
SO MOLECULAR MICROBIOLOGY, (2002 Apr) 44 (2) 335-49.
Journal code: 8712028. ISSN: 0950-382X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020426
Last Updated on STN: 20020817
Entered Medline: 20020816
AB Listeria monocytogenes phage endolysins Ply118 and Ply500 share a unique enzymatic activity and specifically hydrolyse Listeria cells at the completion of **virus** multiplication in order to release progeny phage. With the aim of determining the molecular basis for the lytic specificity of these enzymes, we have elucidated their domain structure and examined the function of their unrelated and unique C-terminal cell wall binding domains (CBDs). Analysis of deletion mutants showed that both domains are needed for lytic activity. Fusions of CBDs with green fluorescent protein (GFP) demonstrated that the C-terminal 140 amino acids of Ply500 and the C-terminal 182 residues of Ply118 are necessary and sufficient to direct the murein hydrolases to the bacterial cell wall. CBD500 was able to target GFP to the surface of Listeria cells belonging to serovar groups 4, 5 and 6, resulting in an even staining of the entire cell surface. In contrast, the CBD118 hybrid bound to a **ligand** predominantly present at septal regions and cell poles, but only on cells of serovars 1/2, 3 and 7. **Non-covalent** binding to surface carbohydrate **ligands** occurred in a rapid, saturation-dependent manner. We measured 4 x 104 and 8 x 104 binding sites for CBD118 and CBD500 respectively. Surface plasmon resonance analysis revealed unexpected high molecular affinity constants for the CBD-**ligand** interactions, corresponding to nanomolar affinities. In conclusion, we show that the CBDs are responsible for targeting the phage endolysins to their substrates and function to confer recognition specificity on the proteins. As the CBD sequences contain no repeats and lack all known sequence motifs for anchoring of proteins to the bacterial cell, we conclude that they use unique structural motifs for specific association with the surface of Gram-positive bacteria.

L9 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 2001:283986 CAPLUS
DN 134:309693
TI AB5 toxin B subunit mutants with altered chemical conjugation characteristics

IN Handley, Harold H.; Haaparanta, Tapio; Ewalt, Karla L.
PA Active Biotech AB, Swed.
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001027144	A2	20010419	WO 2000-US27607	20001005
WO 2001027144	A3	20020117		

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1222202	A2	20020717	EP 2000-968795	20001005

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

PRAI US 1999-158561P	P	19991008	
WO 2000-US27607	W	20001005	

AB A recombinant AB5 B subunit protein including at least one mutation, wherein the mutation alters the no. of amino acid residues available for chem. modification as compared to a wild type AB5 B subunit protein, and wherein said recombinant protein retains an effective target **ligand** bind affinity. For example, specifically designed mutations are produced in the cholera Toxin B subunit (CTB) such that it can still bind with high affinity to its receptor, Gm-1, but can be specifically covalently linked at lysines or cysteines to an immunogen or vaccine. The vaccine produced from this coupling is a mucosal vaccine which has high immunogenicity due to the interaction with the CTB. The vaccine can be produced inexpensively and easily. Alternatively, a technique is disclosed for treating CTB such that **non-covalent** coupling to a vaccine or immunogen can occur. The disclosed CTB can not only be used as vaccine but also as bioactive mol. delivery agent.

L9 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 2000:157662 CAPLUS
DN 132:204009
TI Nucleic acid transporter systems and their use in cell transformation
IN Woo, Savio L.; Smith, Louis C.; Cristiano, Richard J.; Gottchalk, Stephen; Sparrow, Jim
PA Baylor College of Medicine, USA
SO U.S., 108 pp., Cont.-in-part of U.S. Ser. No. 855,389.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6033884	A	20000307	US 1993-167641	19931214
WO 9318759	A1	19930930	WO 1993-US2725	19930319

W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GR, HU, JP, LU, NL, NO, PL, RO, RU, SE, UA, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, NL

US 5994109	A	19991130	US 1995-460890	19950603
US 6150168	A	20001121	US 1995-460971	19950605
US 6177554	B1	20010123	US 1995-462040	19950605

PRAI US 1992-855389 A2 19920320
WO 1993-US2725 A2 19930319
US 1993-167641 A3 19931214

AB Nucleic acid transporter systems for delivery of nucleic acids to a cell comprising a binding complex, which binding complex contains a binding mol. which **non-covalently** binds to the nucleic acid and covalently links to a surface **ligand**, nuclear **ligand** and/or a lysis agent, is disclosed. The surface **ligand**, nuclear **ligand** and/or lysis agent may be linked to the binding mol. by spacers such as [NH(CH2CH2)nCO]m (n = 1-3, m = 1-20), (CH2CH2SSCH2CH2)n (n = 1-3), and (COCH2C(COOH):CHCONHCH2CH2S). The binding mol. is spermine or a spermine deriv. The surface **ligand** may be folate. The lysis agent is a **virus** (e.g., adenovirus, parainfluenza **virus**), lytic peptide, or lysis peptide (e.g., listeriolysin). Thus, a transporter system comprising adenovirus-polylysine conjugates was used to deliver factor IX-encoding plasmid to hepatocytes for gene therapy of hemophilia B.

RE.CNT 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 2001:32426 CAPLUS
DN 134:53458
TI Universal microarray
IN Song, Ke
PA Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 22 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 1255552	A	20000607	CN 1998-122060	19981201
PRAI	CN 1998-122060		19981201		

AB One universal microarray is prepd. by fixing different biol. or chem. mols.-loading optical fiber or capillary support on the surface of inert matrix such as glass or quartz in a square matrix mode, and used for prepg. gene chip, immune chip, protein chip, cell chip, receptor chip, chem. chip, or material chip. The assemblier is a serial displacers mounted on array cartridge in a type composing mode, and consists of serial and parallel trains on matrix sheet, a magnet opposite a train, a controllable resonant cavity above or below a train, a close track in a train, and electrode for magnet in a cartridge. The train consists of a serial biol. mols.-loading closets. The closet is used as accessible address space for specific aim mol.-loading optical fiber or capillary. A wedge-shaped slit with its width slight more than diam. of optical fiber or external diam. of capillary and its length slight more than that of optical fiber or capillary in a closet is used as fetch channel. The scale of closet being vertical to slit is smaller than the length of capillary, the plane of train is parallel to gravity direction, the output of slit is faced to magnet being parallel to train, and the span between slit and magnet is slight more than diam. of optical fiber or external diam. of capillary. The close track used for dropping of optical fiber or capillary has a gas-inlet at its top and a gas-outlet at its bottom. The chip is prepd. by fixing optical fiber or capillary train with gel, placing in a array mode, hardening, and cutting and polishing the section without aim mols. One detection device for optical signal has high signal-to-noise ratio, and is prepd. by jointing microarray and pixel array of cooled CCD camera with optical fiber bundle matched to the detected microarray in a butt joint mode, and drawing the optical fiber bundle out of cooled chamber. The signal amplification technol. in microarray detection comprises labeling probe with reporter mol., and connecting reporter mol. **ligand** with signal mol.-loaded

microparticles. The surface of aim mol.-loaded quartz or glass is pretreated by liq. phase/gas phase silylation, silylation, and/or **non-covalent** surface adsorption. The microarray is used for gene sequencing, gene expression spectrum anal., gene diagnosis, drug precursor screening, material synthesis and optimization, immunol. detection, and bacterial or viral study and diagnosis.

L9 ANSWER 8 OF 22 MEDLINE DUPLICATE 2
AN 2001100448 MEDLINE
DN 20558096 PubMed ID: 11104694
TI Size of the **ligand** complex between the N-terminal domain of the gene III coat protein and the non-infectious phage strongly influences the usefulness of in vitro selective infective phage technology.
AU Cebe R; Geiser M
CS Novartis Pharma, CTA/PSU, Building WSJ 506.3.14, CH-4000 Basel, Switzerland.
SO BIOCHEMICAL JOURNAL, (2000 Dec 15) 352 Pt 3 841-9.
Journal code: 2984726R. ISSN: 0264-6021.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010201
AB The selective infective phage (SIP) technology allows a rapid positive selection of interacting pairs of biological molecules that restore to non-infectious phages their ability to infect the bacterial host. After a successful infection, the phage is amplified and the DNA encoding the interacting **ligand** is isolated from the phage genome and sequenced. In our studies we have evaluated the usefulness of SIP for the identification and cloning of proteins interacting with a biotinylated target binding to a newly designed adapter molecule consisting of streptavidin fused to the C-terminus of the extracellular domain of the phage minor coat protein III. The new adapter was expressed in Escherichia coli and refolded from inclusion bodies. The two different domains joined within the chimaera were found to be biologically functional. We also demonstrated that **non-covalent** interactions between a non-infectious phage displaying a short peptide, which specifically binds the streptavidin, and the adapter molecule restore phage infectivity. To evaluate the potential of SIP as a general and generic tool for the screening of cDNA libraries that encode the **ligands** displayed at the surface of the phage and binding to biotinylated targets, we have increased both the size of the displayed **ligand** on the phage and the size of the biotinylated target bound to the streptavidin domain of the adapter molecule. In our model systems we show that the size of either the **ligand** or the target is a limiting factor for the technology.

L9 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 1999:166212 CAPLUS
DN 130:205161
TI Synergistic antiviral and antitumor compositions of poly(ADP ribose)transferase (pADPRT) CCHC-oxidizing **ligands** and noncovalent pADPRT-inhibitory **ligands**
IN Kun, Ernest; Mendeleyev, Jerome; Kirsten, Eva
PA Octamer, Inc., USA
SO U.S., 30 pp., Cont.-in-part of U.S. Ser. No. 76,313.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 9
PATENT NO. KIND DATE APPLICATION NO. DATE

```
     ---------------  ----  --------        ---------------  --------
PI   US 5877185       A     19990302        US 1995-377584   19950113
     US 5516941       A     19960514        US 1992-965541   19921102
     US 5464871       A     19951107        US 1993-76313    19930611
     WO 9622791       A1    19960801        WO 1996-US420    19960116
          W:  AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS,
              JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO,
              NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AZ, BY,
              KG, KZ
          RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE,
              IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR,
              NE, SN, TD, TG
     AU 9648975       A1    19960814        AU 1996-48975    19960116
     ZA 9600519       A     19960815        ZA 1996-519      19960123
PRAI US 1991-780809   B2    19911022
     US 1992-893429   B2    19920604
     US 1992-965541   A2    19921102
     US 1993-60409    B2    19930512
     US 1993-76313    A2    19930611
     US 1993-87566    A2    19930702
     US 1995-377584   A     19950123
     WO 1996-US420    W     19960116
OS   MARPAT 130:205161
AB   Synergistic compns. are provided which are useful for inactivating
     viruses or inducing apoptosis in tumor cells and for treating
     cancer or retroviral infections.  Generally, the compns. comprise one or a
     plurality of ligands that oxidatively attack a zinc finger of
     pADPRT in combination with one or a plurality of agents selected from
     agents that decrease cellular levels of glutathione and ligands
     that non-covalently bind to the nicotinamide site of
     pADPRT but do not effect zinc ejection from a zinc finger of pADPRT.
RE.CNT  27    THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9   ANSWER 10 OF 22  CAPLUS  COPYRIGHT 2003 ACS
AN   1998:424269  CAPLUS
DN   129:92578
TI   Oil bodies and associated proteins as affinity matrixes
IN   Moloney, Maurice; Boothe, Joseph; Van Rooijen, Gijs
PA   Sembiosys Genetics Inc., Can.; Moloney, Maurice; Boothe, Joseph; Van
     Rooijen, Gijs
SO   PCT Int. Appl., 94 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.       KIND  DATE            APPLICATION NO.  DATE
     ---------------  ----  --------        ---------------  --------
PI   WO 9827115       A1    19980625        WO 1997-CA951    19971205
          W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
              DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR,
              KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
              PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
              US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
          RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
              GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
              GN, ML, MR, NE, SN, TD, TG
     US 5856452       A     19990105        US 1996-767026   19961216
     AU 9852204       A1    19980715        AU 1998-52204    19971205
     AU 739339        B2    20011011
     BR 9713727       A     20000125        BR 1997-13727    19971205
     CN 1245503       A     20000223        CN 1997-181507   19971205
     EP 1007554       A1    20000614        EP 1997-946991   19971205
          R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
```

IE, SI, LT, LV, FI, RO

	JP 2001506241	T2	20010515	JP 1998-527134	19971205
	ZA 9711237	A	19980706	ZA 1997-11237	19971215
	US 6509453	B1	20030121	US 1999-319275	19990827
PRAI	US 1996-767026	A2	19961216		
	WO 1997-CA951	W	19971205		

AB A method is described for the sepn. of a target mol. from a mixt. The method employs oil bodies and their assocd. proteins as affinity matrixes for the selective, **non-covalent** binding of desired target mols. The oil body proteins may be genetically fused to a **ligand** having specificity for the desired target mol. Native oil body proteins can also be used in conjunction with an oil body protein-specific **ligand** such as an antibody or an oil body binding protein. The method allows the sepn. and recovery of the desired target mols. due to the difference in densities between oil bodies and aq. solns.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 1999:22025 CAPLUS
DN 130:63340
TI Optical sensor unit and procedure for the ultrasensitive detection of chemical or biochemical analytes
IN Sigrist, Hans; Gao, Hui; Kunz, Rino; Duebendorfer, Juerg
PA C.S.E.M. Centre Suisse D'electronique Et De Microtechnique SA, Switz.; Prionics AG
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 886141	A1	19981223	EP 1998-810508	19980603
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	EP 887645	A1	19981230	EP 1997-810399	19970623
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 6346376	B1	20020212	US 1999-309546	19990511
PRAI	EP 1997-810399	A	19970623		
	EP 1998-810508	A	19980609		

AB This document describes an optical sensor unit and a procedure for the specific detection and identification of biomols. at high sensitivity in real fluids and tissue homogenates. High detection limits are reached by the combination of i) label-free integrated optical detection of mol. interactions, ii) the use of specific bioconstituents for sensitive detection, and iii) planar optical transducer surfaces appropriately engineered for suppression of non-specific binding, internal referencing and calibration. Applications include the detection of prion proteins and identification of those biomols. which **non-covalently** interact with surface-immobilized prion proteins and are intrinsically involved in the cause of prion-related disease.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:12791 BIOSIS
DN PREV199900012791
TI Electrospray ionization mass spectrometry for the study of **non-covalent** complexes: An emerging technology.
AU Pramanik, Birendra N. (1); Bartner, Peter L.; Mirza, Urooj A.; Liu, Yan-Hui; Ganguly, Ashit K.

CS (1) Schering-Plough Res. Inst., 2015 Galloping Hill Rd., Kenilworth, NJ 07033 USA
SO Journal of Mass Spectrometry, (Oct., 1998) Vol. 33, No. 10, pp. 911-920. ISSN: 1076-5174.
DT Article
LA English
AB The detection of **non-covalent** complexes in the mass range 19 000-34 000 Da, using electrospray ionization mass spectrometry (ESI-MS), is reviewed. The examples discussed include (1) a protein-**ligand** interaction (ras-GDP), (2) an inhibitor-protein-**ligand** interaction (SCH 54292/SCH 54341-ras-GDP), (3) a protein-protein interaction (gamma-IFN homodimer) and (4) a protein-metal complex (HCV (1-181)-Zn). In each case, the ESI-MS method is capable of releasing the intact **non-covalent** complex from its native solution state into the gas phase in the form of multiply-charge ions. The molecular masses of these complexes were determined with a mass accuracy of better than 0.01%, which is far superior to the traditional methods of sodium dodecyl sulfate polyacrylamide gel electrophoresis and gel permeation chromatography. The method provides the researcher with a quick, reliable and reproducible method for probing difficult biological problems. The key to success in the study of **non-covalent** complexes depends on careful understanding and manipulation of ESI source parameters and sample solution conditions; special care must be taken with the source orifice potential and the solution pH and organic co-solvents must be avoided. This paper also illustrates the usefulness of ESI-MS for addressing biological problems leading to the discovery of new therapeutics; the approach involves the rapid screening of potential drug candidates, such as weakly bound inhibitors.

L9 ANSWER 13 OF 22 MEDLINE DUPLICATE 3
AN 1999077258 MEDLINE
DN 99077258 PubMed ID: 9862442
TI A phage-based system to select multiple protein-protein interactions simultaneously from combinatorial libraries.
AU Rudert F; Woltering C; Frisch C; Rottenberger C; Ilag L L
CS MorphoSys AG, Martinsried/Munich, Germany.. rudert@morphosys.de
SO FEBS LETTERS, (1998 Nov 27) 440 (1-2) 135-40. Journal code: 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199901
ED Entered STN: 19990128
Last Updated on STN: 20000303
Entered Medline: 19990111
AB Selectively infective phage (SIP) can be used to identify protein-protein interactions. SIP was modified to facilitate the simultaneous selection of interacting protein pairs from large combinatorial libraries. An interference-resistant phage was constructed which **non-covalently**, but stably links the genetic information of an interacting pair, encoded separately on phage and phagemid vectors, by co-packaging into heteropolyphages. In a model system, the interaction between a SIP-selected peptide and the intracellular domain of the p75 neurotrophin receptor was detected in the presence of a 10(4)-fold excess of a non-interacting control pair (jun leucine zipper and p75 intracellular domain) via SIP hetero-polyphage transductants. To minimize the redundancy of transductants and to minimize possible **ligand** exchange generated in a solution-based SIP screening, a filter-based in situ infectivity screening was developed. The combination of the above techniques may provide a powerful system for rapid screening of very large sequence spaces.

L9 ANSWER 14 OF 22 MEDLINE DUPLICATE 4
AN 95374677 MEDLINE
DN 95374677 PubMed ID: 7646812
TI A receptor that subserves reovirus binding can inhibit lymphocyte proliferation triggered by mitogenic signals.
AU Saragovi H U; Bhandoola A; Lemercier M M; Akbar G K; Greene M I
CS Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada.
SO DNA AND CELL BIOLOGY, (1995 Aug) 14 (8) 653-64.
Journal code: 9004522. ISSN: 1044-5498.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199509
ED Entered STN: 19951005
Last Updated on STN: 19970203
Entered Medline: 19950925
AB A novel surface receptor complex involved in inhibition of T-cell proliferation is described. Biochemical isolation revealed two **non-covalently** associated proteins of about M(r) 65,000 (p65) and 95,000 (p95). These polypeptides may be related. The p65 form is expressed after cellular activation and replication and is recognized by monoclonal antibody (mAb) 87.92.6 or reovirus hemagglutinin as unnatural **ligands**. The p95 species is associated with tyrosine kinase enzymatic activity. Receptor ligation results in rapid alteration of the phosphotyrosine content of cellular substrates, and this activity correlates with antiproliferative effects. The inhibition of proliferation is a time-dependent reversible arrest at the G1-S phase of the cell cycle. Activation through the T-cell receptor, protein kinase C, or addition of cytokines does not reverse the antiproliferative effect. This receptor complex may define novel features of T-cell proliferation.

L9 ANSWER 15 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 1994:263042 CAPLUS
DN 120:263042
TI DNA transporter system and its use for genetic transformation and gene therapy
IN Smith, Louis C.; Woo, Savio L. C.
PA Baylor College of Medicine, USA
SO PCT Int. Appl., 209 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9318759	A1	19930930	WO 1993-US2725	19930319
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GR, HU, JP, LU, NL, NO, PL, RO, RU, SE, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, NL				
	AU 9339668	A1	19931021	AU 1993-39668	19930319
	AU 671450	B2	19960829		
	EP 632722	A1	19950111	EP 1993-909155	19930319
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 07505283	T2	19950615	JP 1993-516812	19930319
	US 6033884	A	20000307	US 1993-167641	19931214
	US 5994109	A	19991130	US 1995-460890	19950603
	US 6150168	A	20001121	US 1995-460971	19950605
	US 6177554	B1	20010123	US 1995-462040	19950605
PRAI	US 1992-855389	A	19920320		
	WO 1993-US2725	A	19930319		
	US 1993-167641	A3	19931214		

AB A DNA transporter system capable of **non-covalently**

binding to DNA and facilitating the insertion of the DNA into a cell is described. The DNA transporter system includes a binding complex which **non-covalently** binds the DNA. The binding complex includes a mol. that is capable of **non-covalently** binding to the DNA and being covalently linked to a surface **ligand** and to a nuclear **ligand**. The surface **ligand** is capable of binding to a cell surface receptor and the nuclear **ligand** is capable of recognizing and transporting the transporter system through the nuclear membrane. A plurality of these binding complexes are attached to the DNA to facilitate the transport of the DNA into the cell. Addnl., a third binding complex which includes a **virus** can also be **non-covalently** linked to the DNA. The **virus** facilitates the movement of the DNA through the cytoplasm and into the nucleus. Also described are a variety of structures which can be used as part of the transporter system as well as methods of using the transporter system to introduce DNA into cells. A modified oligonucleotide designed to target SV40 vectors to specific cells and then to the nucleus of the targeted cell was prepd. The oligonucleotide, which was linked to an intercalating dye, comprised thymine and 5-Me cytosine. Attached via linkers were **ligands** for cell surface receptors and nuclear localization peptides.

L9 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 5
AN 1994:52430 CAPLUS
DN 120:52430
TI **Non-covalent** complexes of HIV gp120 with CD4 and/or mAbs enhance activation of gp120-specific T clones and provide intermolecular help for anti-CD4 antibody production
AU Manca, Fabrizio; Seravalli, Egilde; Valle, Maria Teresa; Fenoglio, Daniela; Kunkl, Annalisa; Li Pira, Giuseppina; Zolla-Pazner, Susan; Celada, Franco
CS Dep. Immunol., Univ. Genoa, Genoa, 16132, Italy
SO International Immunology (1993), 5(9), 1109-17
CODEN: INIMEN; ISSN: 0953-8178
DT Journal
LA English
AB The liaison between CD4 and gp120 that offers the first entry opportunity to HIV may also provoke perturbations of the immune control of the host with far-reaching immunopathol. consequences. The authors wondered whether a mechanism of intermol. help (T help across the gap of a **non-covalent** bond, in contrast to the intramol. help of carrier to hapten) could break self-tolerance and be the cause of the frequent anti-CD4 autoantibodies found in AIDS patients. To det. whether this hypothesis deserves further testing, the authors designed a series of in vitro and in vivo expts. of increasing complexity, focused on the presentation of gp120 to specific T cells by antigen presenting cells (APC) exposed to the envelope protein in the form of **non-covalent** complexes. Bi-mol. complexes were constructed by allowing gp120 or gp160 to bind specific human mAbs. Tri-mol. complexes were constructed by introducing CD4 as an intermediate **ligand** between gp120 and mouse mAbs specific for CD4. In all cases the use of complexes did enhance the immunogenic capacity of substimulatory doses of gp120 or gp160 by facilitating uptake by APC via Fc receptor and consequent presentation to specific human T cell clones. Help for the prodn. in vivo of anti-CD4 antibodies was obtained from T lymphocytes specific for gp120 when CD4-primed memory B cells were pulsed with CD4 complexed with gp120, thus demonstrating in the mouse the entire cycle of intermol. help via **non-covalent** interaction.

L9 ANSWER 17 OF 22 MEDLINE DUPLICATE 6
AN 93378884 MEDLINE
DN 93378884 PubMed ID: 7690241
TI The CR2/CD19 complex on human B cells contains the src-family kinase Lyn.
AU van Noesel C J; Lankester A C; van Schijndel G M; van Lier R A

CS Department of Clinical Viro-Immunology, Central Laboratory of The Netherlands Red Cross Blood Transfusion Service, Amsterdam.
SO INTERNATIONAL IMMUNOLOGY, (1993 Jul) 5 (7) 699-705.
Journal code: 8916182. ISSN: 0953-8178.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199310
ED Entered STN: 19931029
Last Updated on STN: 19960129
Entered Medline: 19931014
AB The complement receptor 2 (CR2 or CD21) can be found in **non-covalent** association with the B lymphocyte specific CD19 complex at the surface of mature human B cells. Upon ligation of the B cell antigen receptor complex (BCR), members of the CR2-CD19 complex may associate with membrane immunoglobulin (mlg). Moreover, CD19 and CD21 **ligands**, either murine mAb, C3d fragments or Epstein-Barr **virus**, are known to have profound effects on B cell activation. We here show that CD19 is tightly linked to the non-receptor src kinase Lyn and that the CD19 glycoprotein itself serves as a substrate for a yet undefined serine/threonine kinase present within the complex. In the process of antigen recognition, mlg and the CR2-CD19 complex may bind different sites of a complement-opsonized antigenic particle. We hypothesize that in this process, approximation to the BCR allows CD19-associated Lyn kinase to phosphorylate potential substrates within the antigen-receptor complex, thereby effecting its coupling to the intracellular compartment.

L9 ANSWER 18 OF 22 MEDLINE DUPLICATE 7
AN 92164643 MEDLINE
DN 92164643 PubMed ID: 1531631
TI Random mutagenesis of CSF-1 receptor (FMS) reveals multiple sites for activating mutations within the extracellular domain.
AU van Daalen Wetters T; Hawkins S A; Roussel M F; Sherr C J
CS Department of Tumor Cell Biology, St Jude Children's Research Hospital, Memphis, TN 38105.
NC CA21765 (NCI)
CA47064 (NCI)
SO EMBO JOURNAL, (1992 Feb) 11 (2) 551-7.
Journal code: 8208664. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199203
ED Entered STN: 19920417
Last Updated on STN: 20000303
Entered Medline: 19920331
AB Retroviral vectors containing human FMS protooncogene cDNA were reconfigured to allow single-step excision and reinsertion of restriction fragments encoding short segments of the extracellular domain of the colony-stimulating factor 1 receptor (CSF-1R). Fragments ligated into M13 bacteriophages were subjected to random chemical mutagenesis on both strands and recloned into the parental vector to create libraries of FMS genes containing mutations restricted to predefined target cassettes. Transfection of retroviral vector libraries into NIH/3T3 cells gave rise to transformed foci from which cellular DNA was amplified by the polymerase chain reaction (PCR), using primers flanking the mutagenized target sequences. Amplified fragments from individual primary transformants were recloned into intact FMS vector plasmids, and those with transforming activity were subjected to nucleotide sequence analysis. Alternatively, retroviruses rescued from transformed cells by superinfection with helper **virus** were used to generate secondary

transformants containing unique copies of proviral DNA, whose sequences were determined after PCR amplification. Novel activating mutations were identified within sequences separating the third and fourth immunoglobulin-like loops, as well as within **non-covalently** stabilized loop 4 of the CSF-1R extracellular domain. Thus, FMS mutations able to convert human CSF-1R to an active oncoprotein are not restricted to those previously identified at codon 301. This approach should be generally applicable for defining activating mutations in related growth factor receptors, including those for platelet-derived growth factor and Steel factor (KIT **ligand**), in which **ligand**-independent oncoprotein variants have not been identified.

L9 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 1991:119896 CAPLUS
DN 114:119896
TI Redirecting the immune response: **ligand**-mediated immunogenicity
AU Shokat, Kevan M.; Schultz, Peter G.
CS Dep. Chem., Univ. California, Berkeley, CA, 94720, USA
SO Journal of the American Chemical Society (1991), 113(5), 1861-2
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
AB **Viruses** and other pathogens have evolved a no. of strategies for evading recognition by the host immune system. Because the immune response involves recognition of naturally occurring constituents of the viral or cellular target, it is difficult to alter the ability of a pathogen to initiate an immune response. Here is described a new strategy for introducing synthetic or natural immunogenic epitopes onto protein surfaces, such as viral coat proteins. A **ligand** that binds **non-covalently** to a conserved site on the protein surface is used to deliver an invariant highly immunogenic antigen to the protein surface. Two hetero-bifunctional drugs: a CD4-dinitrobenzene conjugate and a biotin-dinitrobenzene conjugate were used to target antibodies and complement factor C1q to the AIDS **virus** envelope protein gp120 and streptavidin, resp. This strategy, **ligand** mediated immunogenicity, suggests that a neutralizing antibody response can be generated against any cellular or viral target for which a selective **ligand** is known.

L9 ANSWER 20 OF 22 MEDLINE DUPLICATE 8
AN 91142702 MEDLINE
DN 91142702 PubMed ID: 1996409
TI Conglutinin binds the HIV-1 envelope glycoprotein gp 160 and inhibits its interaction with cell membrane CD4.
AU Andersen O; Sorensen A M; Svehag S E; Fenouillet E
CS Department of Medical Microbiology, Odense University, Denmark.
SO SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1991 Jan) 33 (1) 81-8.
Journal code: 0323767. ISSN: 0300-9475.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199103
ED Entered STN: 19910412
Last Updated on STN: 19970203
Entered Medline: 19910327
AB The highly glycosylated envelope glycoprotein (gp 160) of human immunodeficiency **virus** (HIV) interacts with the CD4 molecule present on the membrane of CD4+ cells and is involved in the pathobiology of HIV infection. Lectins bind glycoproteins through **non-covalent** interactions with specific hexose residues. The mammalian C-type lectin bovine conglutinin was examined for its ability to interact with recombinant gp160 (rgp160) produced in vaccinia **virus** -infected BHK21 cells. Specific binding of conglutinin to rgp160 was

demonstrated by ELISA. The interaction of bovine conglutinin with rgp160 was calcium-dependent, which is characteristic of the binding of a C-type lectin to its **ligand**, and the binding was inhibited in a dose-dependent manner with N-acetyl-D-glucosamine. Deglycosylation of rgp160 abrogated the conglutinin binding. In addition, conglutinin exerted a dose-dependent inhibition of the binding of rgp160 to the CD4 receptor on CEM 13 cells, as demonstrated by FACS analyses. These results indicate that conglutinin may inhibit the infection with HIV-1 through its interaction with the viral envelope glycoprotein.

L9 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 1990:548399 CAPLUS
DN 113:148399
TI Preparation of microparticles containing a bound enzyme label and a **ligand** for immunochemical analysis
IN Nilsson, Kurt G. I.
PA Swed.
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9004181	A1	19900419	WO 1989-SE539	19891002
	W: JP, US				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	SE 8803496	A	19900404	SE 1988-3496	19881003
	SE 466521	B	19920224		
	SE 466521	C	19920827		
	EP 394398	A1	19901031	EP 1989-910963	19891002
	EP 394398	B1	19941207		
	R: DE, GB				
	US 5405752	A	19950411	US 1994-185213	19940114
	US 5738986	A	19980414	US 1996-730966	19961016
PRAI	SE 1988-3496		19881003		
	WO 1989-SE539		19891002		
	US 1990-548976		19900801		
	US 1994-185213		19940114		
	US 1995-403105		19950313		

AB An immunoassay reagent consists of .gtoreq.1 enzyme and .gtoreq.1 other substance (e.g. antibody, antigen, lectin, etc.) which are (**non**) **covalently** bound to a particle (e.g. polysaccharide, glass, org. or inorg. polymer etc.), which has a low or no soly. in H2O and a diam. .ltoreq.1000 .ANG.. The reagent can be used in ELISA or similar enzymic techniques (e.g. immunohistochem. studies, immunoblotting, etc.) for detg. a cell or a **virus** or other component in a sample. The present method of prepg. the reagent avoids problems assocd. with direct conjugation of enzymes to **ligands**, which results in conjugates heterogeneous in size and structure, and possible loss of enzyme activity or specificity. Peroxidase and antitransferrin antibody were coupled to tresyl-activated silica particles to make a reagent which was used in a sandwich-ELISA for detg. human transferrin.

L9 ANSWER 22 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1984:279593 BIOSIS
DN BA78:16073
TI TTV-1 TTV-2 AND TTV-3 A FAMILY OF **VIRUSES** OF THE EXTREMELY THERMOPHILIC ANAEROBIC SULFUR REDUCING ARCHAEBACTERIUM THERMOPROTEUS-TENAX.
AU JANEKOVIC D; WUNDERL S; HOLZ I; ZILLIG W; GIERL A; NEUMANN H
CS MAX-PLANCK-INST. BIOCHEMIE, D-8033 MARTINSRIED, FRG.
SO MOL GEN GENET, (1983) 192 (1-2), 39-45.
CODEN: MGGEAE. ISSN: 0026-8925.

FS BA; OLD
LA English
AB Three different temperent **viruses** of the extremely thermophilic chemolithoautotrophic archaebacterium, T. tenax, TTV1, TTV2 and TTV3, each contain linear, double-stranded DNA, TTV1 and TTV2 of 16 [kilobase] kb, TTV3 of 27 kb. They are oblong and each consists of an outer envelope and an inner core associated with the DNA. TTV1 contains 4 major proteins, an envelope of unknown nature and nonprotein material linked to 2 of the proteins in a **non-covalent** manner. The 5'-ends of the DNA are protected by hydrophobic **ligands**. The **viruses** have neither homologies with each other nor with the host. Lysogens are induced upon sulfur depletion during autotrophic growth. Sensitive, non-lysogenic cells allow lytic multiplication.

=>

```
=> d his

     (FILE 'HOME' ENTERED AT 18:40:02 ON 03 FEB 2003)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 18:40:14 ON 03 FEB
     2003
L1         17145 S VIRUS AND LIGAND
L2           453 S (MIX? OR MIXTURE)(8A)L1
L3         25253 S (MIX? OR MIXTURE)(8A)(VIRUS OR LIGAND)
L4            87 S L1 AND L3
L5            59 DUP REM L4 (28 DUPLICATES REMOVED)
L6          6006 S NON-COVALENT
L7          9012 S NON-COVALENT?
L8            38 S L1 AND L7
L9            22 DUP REM L8 (16 DUPLICATES REMOVED)
L10      8576710 S PROTEIN OR PRPTIDE OR HORMONE OR ANTIBOD? OR EGF OR FGF OR VE
L11       399195 S L10(S)VIRUS
L12         7965 S MIX?(S)L11
L13            6 S L7 AND L12
L14          212 S L7 AND L11
L15          149 S L7(S)L11
L16            4 DUP REM L13 (2 DUPLICATES REMOVED)
L17           70 DUP REM L15 (79 DUPLICATES REMOVED)
L18      1664636 S ADENOVIR? OR RETROVIR? OR VIRUS
L19          625 S (ALTER? OR MODIF?)(3A)TROPISM
L20          515 S L18(S)L19
L21          293 S L18(6A)L19
L22       750751 S LIGAND
L23          204 S L21 AND L10
L24           58 S L21 AND L22
L25           30 DUP REM L24 (28 DUPLICATES REMOVED)

=> d bib ab 1-30 l25

L25  ANSWER 1 OF 30     MEDLINE                          DUPLICATE 1
AN   2003028014      IN-PROCESS
DN   22422734   PubMed ID: 12536200
TI   Generation of an adenoviral vector containing an addition of a
     heterologous ligand to the serotype 3 fiber knob.
AU   Uil Taco G; Seki Toshiro; Dmitriev Igor; Kashentseva Elena; Douglas Joanne
     T; Rots Marianne G; Middeldorp Jaap M; Curiel David T
CS   Departments of Medicine, Pathology and Surgery, Division of Human Gene
     Therapy, and the Gene Therapy Center, University of Alabama at Birmingham,
     Birmingham, Alabama 35294, USA.
SO   CANCER GENE THERAPY, (2003 Feb) 10 (2) 121-4.
     Journal code: 9432230. ISSN: 0929-1903.
CY   England: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   IN-PROCESS; NONINDEXED; Priority Journals
ED   Entered STN: 20030122
     Last Updated on STN: 20030122
AB   As an initial assessment of the feasibility of employing the adenovirus
     serotype 3 (Ad3) fiber knob as a locale for introducing a tropism
     -modifying motif, we generated an adenoviral vector
     containing a six-histidine tag genetically fused to the carboxy-terminus
     of the Ad3 fiber knob. The heterologous tag proved to be accessible for
     binding in the context of the virion and, moreover, had rendered the
     modified vector capable of mediating gene transfer through an artificial,
     non-Ad3 receptor. Cancer Gene Therapy (2003) 10, 121-124
     doi:10.1038/sj.cgt.7700543

L25  ANSWER 2 OF 30  CAPLUS  COPYRIGHT 2003 ACS
```

AN 2002:240992 CAPLUS
DN 136:274275
TI Virus carrying **ligands** for specific receptors of B-, T- and mast cells for use in targeted gene delivery
IN Van Es, Helmuth Hendrikus Gerardus; Van Zutphen, Marlijn; Ma, Libin; Havenga, Menzo Jans Emko
PA Galapagos Genomics N.V., Belg.; Crucell Holland B.V.
SO PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002024933	A2	20020328	WO 2001-EP11086	20010925
	WO 2002024933	A3	20020711		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1191105	A1	20020327	EP 2000-203375	20000925
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AU 2002020567	A5	20020402	AU 2002-20567	20010925
PRAI	EP 2000-203375	A	20000925		
	US 2001-290403P	P	20010511		
	WO 2001-EP11086	W	20010925		

AB A method of delivering nucleic acids to T lymphocytes, B-, and mast cells that uses a virus with a modified coat protein contg. sequences that bind to cell-specific receptors is described. Specifically, the coat protein contains sequences from the fiber proteins of human adenoviruses 35 or 51 that are **ligands** for said binding receptor. Alternatively, the vector may be an adenovirus with a capsid of a modified capsid protein that contains sequences from a different **adenovirus** that **alter** the cell **tropism** of the **virus**. The present invention also relates to a method for transducing a cell, said cell selected from the group consisting of T lymphocytes, B cells, and mast cells comprising contacting said cells with an adenovirus particle comprising a non-adenovirus nucleic acid sequence and a chimeric capsid protein comprising amino acid sequence derived from at least two adenovirus serotypes, wherein said particle has a greater tropism for said cells relative to at least one of the adenovirus serotypes comprising said chimeric capsid protein. The present invention further relates to transduced cells, arrays of subpopulations of cells, a method for ex vivo transduction of a population of cells comprising and a method of administering to a human or other mammalian animal subject a population of cells genetically modified ex vivo. The present invention further relates to a method for identifying the function of a first nucleic acid in hematopoietic cells. The preferred vectors are adenoviruses that may have other modification to render them replication incompetent or otherwise safe. The construction of adenovirus 5 carrying fiber protein domains from other human adenovirus serotypes is described. A cloning system for the rapid construction of such strains is also described. The effectiveness of the different fiber proteins to direct gene delivery to T lymphocytes was demonstrated using a green fluorescent protein reporter gene. Adenovirus 5 was a poor vector, but replacement of the fiber proteins with those from adenovirus 35 or 51 greatly increased the efficiency of transfection.

L25 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:90081 CAPLUS
DN 136:146147
TI Modified virus
IN Lindholm, Leif; Nord, Anna Karin; Boulanger, Pierre Alain
PA Got-A-Gene AB, Swed.; Gardner, Rebecca
SO PCT Int. Appl., 163 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002008263	A2	20020131	WO 2001-GB3252	20010719
	WO 2002008263	A3	20020613		

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2000-17720 A 20000719

AB The present invention describes a modified virus comprising one or more non-native polypeptides, which polypeptide comprises one or more framework moieties each contg. one or more binding moieties, which polypeptide is capable of being expressed in the cytoplasm and nucleus of a mammalian host cell in a conformation which is maintained in the absence of a **ligand** for said binding moieties, said conformation allowing said binding moieties subsequently to bind with said **ligand**, and which polypeptide is capable of transport through the nuclear membrane, wherein said modified **virus** has an **altered tropism** conferred by said binding moieties and the use of such viruses in the therapy, particularly in the treatment of tumors or other cancerous cells. Thus a fusion protein consisting of Human adenovirus 5 fiber protein A1, the trimerization motif of human lung surfactant D and human epidermal growth factor was constructed and produced in cell culture of Human adenovirus 5..

L25 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:788936 CAPLUS
DN 137:305733
TI Use of coat protein fusion proteins to alter the cell specificity of adenoviruses and the delivery of therapeutic genes
IN Wickham, Thomas J.; Kovesdi, Imre; Brough, Douglas E.
PA Genvec, Inc., USA
SO U.S., 77 pp., Cont.-in-part of U.S. 5,712,136.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6465253	B1	20021015	US 1999-101751	19990129
	US 5559099	A	19960924	US 1994-303162	19940908
	US 5965541	A	19991012	US 1995-563368	19951128
	US 5712136	A	19980127	US 1996-634060	19960417
	US 5846782	A	19981208	US 1996-701124	19960821
	WO 9720051	A2	19970605	WO 1996-US19150	19961127
	WO 9720051	A3	19970828		

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,

ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS,
LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, US, UZ, VN, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,
IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,
MR, NE, SN, TD, TG

US 2003022355 A1 20030130 US 2001-999724 20011024
PRAI US 1994-303162 A2 19940908
US 1995-563368 A2 19951128
US 1996-634060 A2 19960417
US 1996-700124 A2 19960821
US 1996-701124 A2 19960821
WO 1996-US19150 W 19961127
US 1996-700846 A2 19960821
US 1999-101751 A1 19990129

AB Fusion proteins of adenovirus coat proteins (hexon, prenton, or fiber) with non-viral proteins that can be used to redirect the virus to cell types that do not carry the adenovirus receptor CAR are described. The fusion protein can direct cell tropism and uptake to such cell types and increase the efficiency of virus uptake beyond the basal level of CAR receptor-independent uptake. The present invention also provides an adenoviral vector that comprises the chimeric adenovirus coat protein, as well as methods of constructing and using such a vector. Construction of an expression vector for prepn. of chimeric genes for fiber protein fusion products is described. A replication incompetent adenoviral vector that can be used for delivery of foreign DNA that will recombine with the fiber protein vector is also described. The gene for a fiber protein with a lysine oligomer at the C-terminus was constructed and adenovirus particles contg. the protein were propagated. The virus showed efficient binding to receptor-free HS68 cells. The binding could be blocked by anionic materials such as chondroitin sulfate and heparin. It could also be blocked by enzymes that removed anionic moieties from cell surface (heparinase, sialidase).

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 30 MEDLINE DUPLICATE 2
AN 2002152468 MEDLINE
DN 21881908 PubMed ID: 11884580
TI Redirecting retroviral tropism by insertion of short, nondisruptive peptide **ligands** into envelope.
AU Gollan Timothy J; Green Michael R
CS Programs in Gene Function and Expression and in Molecular Medicine, Howard Hughes Medical Institute, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA.
SO JOURNAL OF VIROLOGY, (2002 Apr) 76 (7) 3558-63.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200204
ED Entered STN: 20020311
Last Updated on STN: 20020420
Entered Medline: 20020419
AB A potentially powerful approach for in vivo gene delivery is to target retrovirus to specific cells through interactions between cell surface receptors and appropriately modified viral envelope proteins. Previously, relatively large (>100 residues) protein **ligands** to cell surface receptors have been inserted at or near the N terminus of **retroviral** envelope proteins. Although viral **tropism** could be **altered**, the chimeric envelope proteins lacked full activity, and coexpression of wild-type envelope was required for

production of transducing virus. Here we analyze more than 40 derivatives of ecotropic Moloney murine leukemia virus (MLV) envelope, containing insertions of short RGD-containing peptides, which are **ligands** for integrin receptors. In many cases pseudotyped viruses containing only the chimeric envelope protein could transduce human cells. The precise location, size, and flanking sequences of the **ligand** affected transduction specificity and efficiency. We conclude that retroviral tropism can be rationally reengineered by insertion of short peptide **ligands** and without the need to coexpress wild-type envelope.

L25 ANSWER 6 OF 30 MEDLINE DUPLICATE 3
AN 2002457068 IN-PROCESS
DN 22204059 PubMed ID: 12215264
TI Genetic **modification** of **adenovirus** 5 **tropism** by a novel class of **ligands** based on a three-helix bundle scaffold derived from staphylococcal protein a.
AU Henning P; Magnusson M K; Gunneriusson E; Hong S S; Boulanger P; Nygren P-A; Lindholm L
CS Department of Medical Microbiology and Immunology, University of Goteborg, SE-405 30 Goteborg, Sweden and Got-A-Gene AB, SE-412 92 Goteborg, Sweden.
SO HUMAN GENE THERAPY, (2002 Aug) 13 (12) 1427-39. Journal code: 9008950. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020907
Last Updated on STN: 20021212
AB The use of adenovirus (Ad) as an efficient and versatile vector for in vivo tumor therapy requires the modulation of its cellular tropism. We previously developed a method to genetically alter the tropism of Ad5 fibers by replacing the fiber knob domain by an extrinsic trimerization motif and a new cellular **ligand**. However, fibers carrying complex **ligands** such as single-chain antibody fragments did not assemble into functional pentons in vitro in the presence of penton base, and failed to be rescued into infectious virions because of their inability to fold correctly within the cytoplasm of Ad-infected cells. Here we show that the coding sequence for a disulfide bond-independent three-helix bundle scaffold Z, derived from domain B of Staphylococcal protein A and capable of binding to the Fc portion of immunoglobulin (Ig) G1, could be incorporated into modified knobless Ad fiber gene constructs with seven shaft repeats. These fiber gene constructs could be rescued into viable virions that were demonstrated to enter 293 cells engineered for IgG Fc surface expression but not unmodified 293 cells, via a mechanism that could be specifically blocked with soluble Fc target protein. However, the **tropism modified viruses** showed a slightly impaired cellular entry and a lower infectivity than wildtype (WT) virus. In addition, we generated recombinant fibers containing an IgA binding Affibody(TM) **ligand**, derived from combinatorial specificity-engineering of the Z domain scaffold. Such fiber constructs also showed the expected target specific binding, indicating that the affibody protein class is ideally suited for genetic engineering of Ad tropism.

L25 ANSWER 7 OF 30 MEDLINE DUPLICATE 4
AN 2002433487 IN-PROCESS
DN 22177695 PubMed ID: 12189716
TI **Tropism-modified adenoviral** and adeno-associated viral vectors for gene therapy.
AU Nicklin Stuart A; Baker Andrew H
CS BHF Blood Pressure Group, Department of Medicine and Therapeutics, University of Glasgow, Western Infirmary, Church Street, Glasgow G11 6NT, UK.
SO Curr Gene Ther, (2002 Sep) 2 (3) 273-93.

Journal code: 101125446. ISSN: 1566-5232.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020823
Last Updated on STN: 20021212
AB One of the most rapidly advancing areas of gene therapy is vector development. For the majority of gene therapy procedures, efficient and selective transduction would provide safe and more effective treatments at optimal vector doses. Advances in vector targeting strategies have been rapid within the field of DNA-based viruses, particularly adenovirus (Ad) and more recently adeno-associated virus (AAV) based vectors. Vector targeting at the level of virus: cell interaction can be achieved using both non-genetic and genetic methodology. Non-genetic approaches typically utilise bispecific antibodies that both neutralise wild-type virus tropism and provide a new cell binding capacity. For genetic targeting strategies, the virus capsid can be engineered to express foreign **ligands** that target selected receptors in the absence or presence of additional modification to ablate the virus' natural tropism. This review covers technological advances that have led to targeting of Ad and AAV and highlights the potential for these 'designer' viruses for future gene-based therapeutics.

L25 ANSWER 8 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:396897 CAPLUS
DN 135:15084
TI Adenoviruses with altered fiber proteins giving them lower affinity for their endogenous cellular receptor and the alteration of cell tropism
IN Legrand, Valerie; Leissner, Philippe
PA Transgene S.A., Fr.
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001038361	A1	20010531	WO 2000-FR3263	20001123
	W: AU, CA, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
	EP 1242449	A1	20020925	EP 2000-985308	20001123
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	FR 1999-14842	A	19991125		
	WO 2000-FR3263	W	20001123		

AB Adenoviruses that have a reduced affinity for their endogenous CAR (coxsackie/adenovirus) receptor that have mutations affecting a small 14-amino acid peptide of the fiber protein are described. These viruses can be used to create new **adenoviruses** with **altered** cell **tropisms** without a residual tropism from the fiber protein. A human adenovirus 5 variant carrying a peptide derived from gastrin-releasing peptide in the fiber protein was constructed. The infection of 3T3 cells by virus carrying a wild-type fiber could be blocked by empty adenovirus heads. However, the virus carrying the gastrin-releasing peptide in the fiber was resistant to interference by the same mechanism. After inactivation of receptor binding by the fiber, it was found that tropism could be altered by incorporating the **ligand** into the hexon protein of the viral head. A series of possible substitutions in the the C-terminal domain of the fiber protein is described.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 9 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:168166 CAPLUS
DN 134:219642
TI Adenoviruses with altered fiber proteins giving them lower affinity for their endogenous cellular receptor and the alteration of cell tropism
IN Van Raaij, Mark Johan; Cusack, Stephen; Legrand, Valerie; Leissner, Philippe; Mehtali, Majid
PA Transgene S.A., Fr.; European Molecular Biology Laboratory (EMBL)
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001016344	A1	20010308	WO 2000-FR2377	20000825
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1124977	A1	20010822	EP 2000-958742	20000825
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI FR 1999-10859	A	19990827		
WO 2000-FR2377	W	20000825		

AB Adenoviruses that have a reduced affinity for their endogenous CAR (coxsackie/adenovirus) receptor that have mutations affecting the A and B layers and AB loop of the protein are described. These viruses can be used to create new **adenoviruses** with **altered** cell **tropisms** without a residual tropism from the fiber protein. A human adenovirus 5 variant carrying a peptide derived from gastrin-releasing peptide in the fiber protein was constructed. The infection of 3T3 cells by virus carrying a wild-type fiber could be blocked by empty adenovirus heads. However, the virus carrying the gastrin-releasing peptide in the fiber was resistant to interference by the same mechanism. After inactivation of receptor binding by the fiber, it was found that tropism could be altered by incorporating the **ligand** into the hexon protein of the viral head.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 10 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:31532 CAPLUS
DN 134:111234
TI Recombinant **adenovirus** vector with changed **tropism** due to **altered** fiber for use in gene therapy
IN Lindholm, Leif
PA Got-A-Gene, Swed.
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001002431	A1	20010111	WO 2000-SE1390	20000630
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,				

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1196435 A1 20020417 EP 2000-946680 20000630

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRAI SE 1999-2601 A 19990706

US 1999-143632P P 19990714

WO 2000-SE1390 W 20000630

AB The present invention relates to new recombinant adenovirus with changed tropism. In the adenovirus the native fiber protein, comprising a fiber tail, a fiber shaft and a fiber knob including a trimerization motif, has been changed in that the native knob contg. the cell binding structure and the native trimerization motif has been removed and a new cell-binding **ligand** and an external trimerization motif have been introduced into the virus fiber. The invention also relates to the recombinant adenovirus for the treatment of human diseases, either in vivo or by in vitro methods. Also included is a method for rescuing of recombinant adenovirus fibers into the adenovirus genome.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 11 OF 30 MEDLINE DUPLICATE 5

AN 2001196602 MEDLINE

DN 21126423 PubMed ID: 11222722

TI Adenovirus type 5 viral particles pseudotyped with mutagenized fiber proteins show diminished infectivity of coxsackie B-adenovirus receptor-bearing cells.

AU Jakubczak J L; Rollence M L; Stewart D A; Jafari J D; Von Seggern D J; Nemerow G R; Stevenson S C; Hallenbeck P L

CS Genetic Therapy, Inc./A Novartis Company, Gaithersburg, Maryland 20878, USA.

SO JOURNAL OF VIROLOGY, (2001 Mar) 75 (6) 2972-81.
Journal code: 0113724. ISSN: 0022-538X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200104

ED Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405

AB A major limitation of adenovirus type 5 (Ad5)-based gene therapy, the inability to target therapeutic genes to selected cell types, is attributable to the natural tropism of the virus for the widely expressed coxsackievirus-adenovirus receptor (CAR) protein. Modifications of the Ad5 fiber knob domain have been shown to **alter** the **tropism** of the **virus**. We have developed a novel system to rapidly evaluate the function of modified fiber proteins in their most relevant context, the adenoviral capsid. This transient transfection/infection system combines transfection of cells with plasmids that express high levels of the modified fiber protein and infection with Ad5.beta gal.Delta F, an E1-, E3-, and fiber-deleted adenoviral vector encoding beta-galactosidase. We have used this system to test the adenoviral transduction efficiency mediated by a panel of fiber protein mutants that were proposed to influence CAR interaction. A series of amino acid modifications were incorporated via mutagenesis into the fiber expression plasmid, and the resulting fiber proteins were subsequently incorporated onto adenoviral particles. Mutations located in the fiber knob AB and CD loops demonstrated the greatest reduction in fiber-mediated gene transfer in HeLa cells. We also observed effects on transduction efficiency with mutations in the FG loop, indicating that the binding site may extend to the adjacent monomer in the fiber trimer and in the HI loop. These studies support the concept that modification of the fiber knob domain to diminish or ablate CAR interaction should result in a detargeted adenoviral vector

that can be combined simultaneously with novel **ligands** for the development of a systemically administered, targeted adenoviral vector.

L25 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:553697 CAPLUS
DN 133:145909
TI **Altering** the cell **tropism** of **adenoviral** vectors by modification or substitution of the receptor-binding domain of the fiber and the use of novel receptors
IN Curiel, David T.; Krasnykh, Victor N.; Dmitriev, Igor; Douglas, Joanne T.
PA UAB Research Foundation, USA
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000046364	A1	20000810	WO 2000-US2867	20000203

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1999-118880P P 19990205

AB The present invention provides a means for the propagation of adenovirus lacking the native tropism by using genetic methods to modify the fiber protein by addn. of a C-terminal tag. The modified virus is then propagated in a cell line transfected with a sequence encoding an artificial receptor for the C-terminal tag on the modified fiber protein. The use of single-chain antibodies and of peptides binding the knob of adenovirus 5 in novel receptors is demonstrated. The knob-binding peptide was identified by screening of a phage display library with the adenovirus knob. Fiber receptor-neg. cells expressing genes for these receptors could be infected with adenovirus. Methods for the incorporation of novel peptides into the HI loop of the knob protein are described and the incorporation of a hexahistidine loop is demonstrated. A single-chain antibody to hexahistidine was used to develop a receptor.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:172980 CAPLUS
DN 132:204637
TI Tissue-binding peptides identified in display libraries for diagnostic and therapeutic use
IN Schrader, Juergen; Herrmann, Andreas
PA Germany
SO Ger., 24 pp.
CODEN: GWXXAW
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 19845434	C1	20000316	DE 1998-19845434	19981002
CA 2345214	AA	20000413	CA 1999-2345214	19991001
WO 2000020572	A2	20000413	WO 1999-EP7296	19991001
WO 2000020572	A3	20000720		

W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

EP 1117775	A2	20010725	EP 1999-948916	19991001

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRAI DE 1998-19845434 A 19981002

WO 1999-EP7296 W 19991001

AB Peptides that bind specifically to different tissue types are identified in display libraries for use in the diagnosis of disease or in the targeted delivery of drugs (no data). A com. bacterial display library contg. .apprx.109 random peptides was incubated with a section of rat carotid artery that was recovering from exptl. induced restenosis. Bound cells were washed from the tissue, plated and screened again. The binding peptides were characterized after five rounds of selection.

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 14 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:408876 BIOSIS
DN PREV200000408876
TI Mutational analysis of the adeno-associated virus type 2 (AAV2) capsid gene and construction of AAV2 vectors with altered tropism.
AU Wu, Pei; Xiao, Wu; Conlon, Thomas; Hughes, Jeffrey; Agbandje-McKenna, Mavis; Ferkol, Thomas; Flotte, Terence; Muzyczka, Nicholas (1)
CS (1) Department of Molecular Genetics and Microbiology, College of Medicine, University of Florida, Gainesville, FL, 32610 USA
SO Journal of Virology, (September, 2000) Vol. 74, No. 18, pp. 8635-8647. print.
ISSN: 0022-538X.
DT Article
LA English
SL English

AB Adeno-associated virus type 2 (AAV2) has proven to be a valuable vector for gene therapy. Characterization of the functional domains of the AAV capsid proteins can facilitate our understanding of viral tissue tropism, immunoreactivity, viral entry, and DNA packaging, all of which are important issues for generating improved vectors. To obtain a comprehensive genetic map of the AAV capsid gene, we have constructed 93 mutants at 59 different positions in the AAV capsid gene by site-directed mutagenesis. Several types of mutants were studied, including epitope tag or **ligand** insertion mutants, alanine scanning mutants, and epitope substitution mutants. Analysis of these mutants revealed eight separate phenotypes. Infectious titers of the mutants revealed four classes. Class 1 mutants were viable, class 2 mutants were partially defective, class 3 mutants were temperature sensitive, and class 4 mutants were noninfectious. Further analysis revealed some of the defects in the class 2, 3, and 4 mutants. Among the class 4 mutants, a subset completely abolished capsid formation. These mutants were located predominantly, but not exclusively, in what are likely to be beta-barrel structures in the capsid protein VP3. Two of these mutants were insertions at the N and C termini of VP3, suggesting that both ends of VP3 play a role that is important for capsid assembly or stability. Several class 2 and 3 mutants produced capsids that were unstable during purification of viral particles. One mutant, R432A, made only empty capsids, presumably due to a defect in packaging viral DNA. Additionally, five mutants were defective in heparan binding, a step that is believed to be essential for viral entry. These were distributed into two amino acid clusters in what is likely to be a cell surface loop in the capsid protein VP3. The first cluster spanned amino acids 509 to 522; the second was between amino acids 561 and 591. In addition to the heparan binding clusters, hemagglutinin epitope tag insertions identified several other regions that were on the surface of the capsid. These included insertions at amino acids 1, 34, 138, 266, 447, 591, and 664. Positions 1 and 138 were the N termini of VP1 and VP2, respectively; position 34 was exclusively in VP1; the remaining surface positions were located in putative loop regions of VP3. The remaining mutants, most of them partially defective, were presumably defective in steps of viral entry that were not tested in the preliminary screening, including intracellular trafficking, viral uncoating, or coreceptor binding. Finally, in vitro experiments showed that insertion of the serpin receptor **ligand** in the N-terminal regions of VP1 or

VP2 can change the tropism of AAV. Our results provide information on AAV capsid functional domains and are useful for future design of AAV vectors for targeting of specific tissues.

L25 ANSWER 15 OF 30 MEDLINE DUPLICATE 6
AN 2000387890 MEDLINE
DN 20347350 PubMed ID: 10888627
TI Ectodomain of coxsackievirus and adenovirus receptor genetically fused to epidermal growth factor mediates adenovirus targeting to epidermal growth factor receptor-positive cells.
AU Dmitriev I; Kashentseva E; Rogers B E; Krasnykh V; Curiel D T
CS Division of Human Gene Therapy, Departments of Medicine, Pathology, and Surgery, Gene Therapy Center, University of Alabama at Birmingham, Birmingham, Alabama 35294-3300, USA.
NC RO1 CA68245 (NCI)
RO1 CA74242 (NCI)
RO1 HL50255 (NHLBI)
+
SO JOURNAL OF VIROLOGY, (2000 Aug) 74 (15) 6875-84.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 20000818
Last Updated on STN: 20001005
Entered Medline: 20000810
AB Human adenovirus (Ad) is extensively used for a variety of gene therapy applications. However, the utility of Ad vectors is limited due to the low efficiency of Ad-mediated gene transfer to target cells expressing marginal levels of the Ad fiber receptor. Therefore, the present generation of Ad vectors could potentially be improved by **modification** of Ad **tropism** to target the **virus** to specific organs and tissues. The fact that coxsackievirus and adenovirus receptor (CAR) does not play any role in virus internalization, but functions merely as the virus attachment site, suggests that the extracellular part of CAR might be utilized to block the receptor recognition site on the Ad fiber knob domain. We proposed to design bispecific fusion proteins formed by a recombinant soluble form of truncated CAR (sCAR) and a targeting **ligand**. In this study, we derived sCAR genetically fused with human epidermal growth factor (EGF) and investigated its ability to target Ad infection to the EGF receptor (EGFR) overexpressed on cancer cell lines. We have demonstrated that sCAR-EGF protein is capable of binding to Ad virions and directing them to EGFR, thereby achieving targeted delivery of reporter gene. These results show that sCAR-EGF protein possesses the ability to effectively retarget Ad via a non-CAR pathway, with enhancement of gene transfer efficiency.

L25 ANSWER 16 OF 30 MEDLINE
AN 2001124245 MEDLINE
DN 21028061 PubMed ID: 11156365
TI Advanced generation adenoviral vectors possess augmented gene transfer efficiency based upon coxsackie adenovirus receptor-independent cellular entry capacity.
AU Krasnykh V; Dmitriev I; Navarro J G; Belousova N; Kashentseva E; Xiang J; Douglas J T; Curiel D T
CS Department of Medicine, Gene Therapy Center, The University of Alabama at Birmingham, 35294-3300, USA.
NC R01 CA68245-01 (NCI)
R01 CA74242 (NCI)
R01 HL50255 (NHLBI)
SO CANCER RESEARCH, (2000 Dec 15) 60 (24) 6784-7. Ref: 40
Journal code: 2984705R. ISSN: 0008-5472.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222
AB Adenoviral (Ad) vectors have been widely used in the context of cancer gene therapy approaches. Their utility in these contexts, however, has frequently been limited by tumor cell resistance to Ad infection. The basis of this resistance has been defined recently as resulting from a deficiency of the primary adenovirus receptor, coxsackie adenovirus receptor. As a means to circumvent this limitation, a variety of **tropism modification** strategies have allowed coxsackie **adenovirus** receptor-independent gene delivery via the Ad vector. These advanced generation adenovirus vectors exhibit enhanced infectivity, which can allow direct therapeutic gain. Such vectors may allow improvements in efficacy in the context of ongoing human clinical gene therapy approaches for cancer.

L25 ANSWER 17 OF 30 MEDLINE DUPLICATE 7
AN 2000110570 MEDLINE
DN 20110570 PubMed ID: 10646650
TI Fibroblast growth factor 2-retargeted adenoviral vectors exhibit a modified biolocalization pattern and display reduced toxicity relative to native adenoviral vectors.
AU Printz M A; Gonzalez A M; Cunningham M; Gu D L; Ong M; Pierce G F; Aukerman S L
CS Selective Genetics, Inc., San Diego, CA 92121, USA..
mprintz@selectivegenetics.com
SO HUMAN GENE THERAPY, (2000 Jan 1) 11 (1) 191-204.
Journal code: 9008950. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000211
AB Targeted vectors provide a number of advantages for systemic and local gene delivery strategies. Several groups have investigated the utility of using various **ligands** to **alter** the **tropism** of **adenovirus** (Ad) vectors. We have previously demonstrated that fibroblast growth factor (FGF) **ligands** can specifically target DNA transfection and Ad transduction through high-affinity FGF receptors (FGFRs). FGFRs are overexpressed in abnormally proliferating tissues, such as malignancies. The present studies explore the effects of retargeting with FGF2 on the tissue localization pattern and the systemic toxicity of Ad in mice. Results of semiquantitative PCR analyses indicate that the distribution of FGF2-Ad vector genome sequences after intravenous administration in mice is altered. Markedly lower amounts (10- to 20-fold) of FGF2-Ad localize to the liver when compared with native Ad. This decrease in liver deposition translates into a significant reduction in subsequent toxicity as measured by serum transaminases and histopathology in mice injected with FGF2-AdHSV-thymidine kinase with and without ganciclovir administration. In an intraperitoneal model of ovarian cancer, FGF2-Ad generates increased transgene expression in tumor tissue when compared with Ad. Taken together, these results indicate that the retargeting of Ad with FGF2 results in a more efficient vector system for systemic and regional gene therapy applications, with concomitant lower

levels of systemic toxicity.

L25 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:529241 CAPLUS
DN 131:140498
TI Modified adenovirus contg. a chimeric fiber protein, and uses thereof for cancer therapy
IN Curiel, David T.; Krasnykh, Victor N.
PA The UAB Research Foundation, USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9941359	A1	19990819	WO 1999-US3233	19990216
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2321135	AA	19990819	CA 1999-2321135	19990216
	AU 9932940	A1	19990830	AU 1999-32940	19990216
	AU 751542	B2	20020822		
	BR 9908018	A	20001024	BR 1999-8018	19990216
	EP 1070118	A1	20010124	EP 1999-932506	19990216
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 6210946	B1	20010403	US 1999-250580	19990216
	JP 2002503459	T2	20020205	JP 2000-531540	19990216
	NO 2000004563	A	20000913	NO 2000-4563	20000913
PRAI	US 1998-74844P	P	19980217		
	WO 1999-US3233	W	19990216		

AB The present invention provides means to **modify** the **tropism** of recombinant **adenoviral** vectors using genetic methods to alter the adenoviral fiber cell-binding protein while maintaining the native trimeric protein biosynthesis profile. The present invention further provides means to specifically target particular cell types for infection with said recombinant adenoviral vectors. In a preferred embodiment, the recombinant adenovirus vector comprises fiber replacement proteins composed of the fiber tail domain, a portion of the fibritin gene from the bacteriophage T4, and a **ligand** domain. The vector may also encode a therapeutic gene, such as the herpes simplex virus thymidine kinase gene which, along with ganciclovir, can be used to specifically kill tumor cells.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 19 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:511046 CAPLUS
DN 131:161614
TI Adenovirus vector contg. a heterologous peptide epitope in the HI loop of the fiber knob for gene targeting
IN Curiel, David T.; Krasnykh, Victor N.; Dmitriev, Igor
PA The Uab Research Foundation, USA
SO PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9939734	A1	19990812	WO 1999-US2549	19990205
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2327545	AA	19990812	CA 1999-2327545	19990205
	AU 9926595	A1	19990823	AU 1999-26595	19990205
	AU 744252	B2	20020221		
	BR 9908613	A	20001031	BR 1999-8613	19990205
	EP 1053013	A1	20001122	EP 1999-906761	19990205
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002507391	T2	20020312	JP 2000-530231	19990205
	US 2002081280	A1	20020627	US 1999-245603	19990205
	NO 2000003956	A	20001005	NO 2000-3956	20000804
PRAI	US 1998-73947P	P	19980206		
	US 1998-99801P	P	19980910		
	WO 1999-US2549	W	19990205		

AB The present invention provides means to **modify** the **tropism** of recombinant **adenoviral** vectors using genetic methods to alter the adenoviral fiber cell-binding protein. The present invention generates an adenovirus with a modified fiber gene such that a novel tropism is achieved. This recombinant adenovirus has a fiber gene modified in the HI loop domain.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 20 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:119734 CAPLUS
DN 130:178399
TI Cell-specific **ligand**-antifiber antibody fusion complexed with **adenovirus** vector to **alter adenoviral tropism**
IN Curiel, David T.
PA UAB Research Foundation, USA
SO U.S., 41 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5871727	A	19990216	US 1996-761242	19961206
PRAI	US 1996-761242		19961206		

AB The present invention provides means to **modify** the **tropism** of recombinant **adenoviral** vectors by using antifiber antibody or antibody fragment fused to a cell-specific **ligand**. The targeted vector may be used to deliver a therapeutic gene (such as thymidine kinase) to cancer cells. Thus, an adenovirus 5 vector contg. the herpes simplex virus thymidine kinase gene was complexed with anti-fiber Fab fragment conjugated to folate. When folate receptor-expressing KB cells were incubated with this vector complex and ganciclovir, 73% cell death was obsd. Inclusion of antibody or folate in the incubation medium inhibited this cell killing. Generation of a recombinant adenovirus with modified fiber gene using a two-plasmid rescue system was also demonstrated.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 21 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:728819 CAPLUS
DN 132:74062
TI Dressing up a**denoviruses** to **modify** their **tropism**
AU Paillard, Florence
CS USA
SO Human Gene Therapy (1999), 10(16), 2575-2576
CODEN: HGTHE3; ISSN: 1043-0342
PB Mary Ann Liebert, Inc.
DT Journal; General Review
LA English
AB A review and discussion with 4 refs. on the research of Romanczuk et al. (ibid., 2615-2626) on using peptide **ligands** binding to airway epithelial cells to target adenovirus vectors. The peptides are identified using phage display libraries; the peptide is linked to the virus by way of a bifunctional polyethylene glycol mol.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 22 OF 30 MEDLINE DUPLICATE 8
AN 1999096940 MEDLINE
DN 99096940 PubMed ID: 9878423
TI **Modification** of **retroviral tropism** by display of IGF-I.
AU Chadwick M P; Morling F J; Cosset F L; Russell S J
CS Cambridge MRC Laboratory of Molecular Biology, Hills Road, Cambridge, CB2 2QH, UK.. mpc@kasmir.keme.co.uk
SO JOURNAL OF MOLECULAR BIOLOGY, (1999 Jan 15) 285 (2) 485-94.
Journal code: 2985088R. ISSN: 0022-2836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
ED Entered STN: 19990324
Last Updated on STN: 20000303
Entered Medline: 19990311
AB We have displayed insulin-like growth factor I (IGF-I) as an N-terminal extension of 4070A (amphotropic) retroviral envelope protein. Western blot demonstrated that chimaeric envelope proteins were incorporated into retroviral particles. Interaction between the displayed IGF-I and cell-surface receptors impaired gene delivery. The magnitude of this inhibitory effect was smallest on NIH 3T3 cells, greater on NIH 3T3 cells over-expressing insulin receptor, and greatest on NIH 3T3 cells over-expressing human type-I IGF receptor. Hence, both the number of **ligand** receptors and their affinity for the displayed **ligand** influenced the level of gene delivery. The inhibitory effect was abrogated by cleaving the displayed domain from the underlying envelope protein with factor Xa protease, and by the addition of free **ligand** to the infection. Addition of IGF-I or insulin caused a dose-dependent increase in titre. Possible mechanisms for receptor-mediated inhibition of gene delivery by IGF-displaying vectors are discussed, together with the implications of these results for practical applications of retroviral display and for understanding the mechanism of virus entry.

L25 ANSWER 23 OF 30 MEDLINE DUPLICATE 9
AN 2000131864 MEDLINE
DN 20131864 PubMed ID: 10667212
TI Strategies to adapt adenoviral vectors for targeted delivery.
AU Curiel D T

CS Gene Therapy Center, University of Alabama at Birmingham 35294-3300, USA.. david.curiel@ccc.uab.edu
NC HL50255 (NHLBI)
R01CA68245 (NCI)
R01CA74242 (NCI)
SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1999) 886 158-71. Ref: 52
Journal code: 7506858. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000229
AB The utility of current generation adenoviral vectors for targeted, cell-specific gene delivery is limited by the promiscuous tropism of the parent virus. To address this issue, we have developed both genetic and immunologic methods to alter viral tropism. Immunologic retargeting has been achieved via conjugates comprised of an antifiber knob Fab and a targeting moiety consisting of a **ligand** or antireceptor antibody. Gene delivery by this approach has been accomplished via a variety of cellular pathways including receptors for folate, FGF, and EGF. In addition to cell-specific gene delivery, this strategy has allowed enhanced gene delivery to target cells lacking the native adenoviral receptor, CAR. Of note, this specific and extended gene delivery allowed enhanced survival in murine models of human carcinoma via cancer gene therapy. Genetic strategies to **alter adenoviral tropism** have included both fiber modification and fiber replacement. In the former, we have identified the HI loop of fiber as a propitious locale for introduction of heterologous peptides. Incorporation of an RGDC peptide at this locale allowed gene delivery via cellular integrins with dramatic efficiency augmentations. As a strategy to achieve both new tropism as well as to ablate native tropism, methods have been developed to replace the fiber protein with heterologous motif which preserves the key trimeric quaternary structure of fiber and allows for propagation. Such a fiber-replacement virus has been rescued and has demonstrated capacities consistent with its utility as a novel vector agent. These strategies have allowed the achievement of cell-specific gene delivery via adenoviral vectors and thus have the potential to enhance the utility of this vector agent.

L25 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1998:640334 CAPLUS
DN 129:255990
TI **Adenoviral** vectors with chimeric fiber proteins for **altered** cell **tropism** as well as vector purification
IN Curiel, David T.; Krasnykh, Victor; Dimitriev, Igor
PA UAB Research Foundation, USA
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9841618	A1	19980924	WO 1998-US3879	19980313
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	AU 9864429	A1	19981012	AU 1998-64429	19980313
PRAI	US 1997-40703P	P	19970314		
	US 1997-54112P	P	19970729		
	WO 1998-US3879	W	19980313		

AB The utility of current recombinant adenovirus vectors for gene therapy applications is improved by designing targeted vectors capable of gene delivery to selected cell types in vivo. In order to achieve such targeting, incorporation of **ligands** in the adenoviral fiber protein, in which the protein mediates primary binding of adenovirus to its cell surface receptor, utilizes the HI loop of the fiber knob as a convenient locale for incorporation of heterologous **ligands**. Recombinant fiber proteins expressed in a variety of cells including baculovirus-infected insect cells and E. coli to demonstrate that the incorporation of the FLAG octapeptide into the HI loop does not ablate fiber trimerization and does not disturb formation of the cell-binding site localized in the knob. A recombinant adenovirus of the instant invention having this modified fiber shows that a short peptide sequence engineered in the knob is compatible with the biol. functions of the fiber. A peptide incorporated into the knob according to the invention remains available for binding in the context of mature virions contg. modified fibers. The invention incorporates heterologous **ligands** into the HI loop of the fiber knob and the properties of this locale are consistent with its employment in adenovirus re-targeting strategies.

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 25 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1998:621330 CAPLUS
DN 129:240871
TI **Adenoviral** vectors with **modified tropism** for gene therapy
IN Sosnowski, Barbara A.; Baird, Andrew; Pierce, Glenn F.; Curiel, David T.; Douglas, Joanne T.; Rogers, Buck E.
PA USA
SO PCT Int. Appl., 205 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9840508	A1	19980917	WO 1998-US4964	19980313
	W: AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9864629	A1	19980929	AU 1998-64629	19980313
	AU 742365	B2	20020103		
	EP 973926	A1	20000126	EP 1998-910375	19980313
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001515493	T2	20010918	JP 1998-539848	19980313
PRAI	US 1997-40782P	P	19970314		
	US 1997-65265P	P	19971110		
	WO 1998-US4964	W	19980313		

AB The present invention relates to gene therapy. In particular, therapeutic agents, therapeutic gene products, and compns. are disclosed. Various

systems and methods useful in targeting and delivering non-native nucleotide sequences to specific cells are disclosed, wherein virus-antibody-**ligand** conjugates are used to facilitate targeting and delivery. Thus, FAB-fibroblast growth factor 2 conjugates are constructed by linking modified recombinant fibroblast growth factor (FGF) with the FAB fragment from a blocking monoclonal antibody, 1D6.14, which was generated against adenovirus type 5 knob region. FGF2 retargeting of an **adenovirus** (i.e., **altering** the **tropism** of an **adenovirus** using a fibroblast growth factor) significant enhances targeting efficiency and nuclear trafficking of the adenovirus vector well above that seen when the vector retains its native adenoviral tropism. In addn., FGF retargeting increases the infectability of adenovirus in various cells (e.g., cells expressing Kaposi's sarcoma) compared to the use of native adenovirus tropism alone, even in cell lines hat are resistant to adenovirus infection. The use of FGF retargeting vectors enhances potency; FGF-retargeted vectors deliver and promote the expression of a therapeutic gene to more target cells and in each cell so targeted. The vectors of the present invention are also significantly less toxic to the liver and are less immunogenic than are other adenovirus vectors. Finally, retargeting the viral vector retarged with FGF induces cytotoxicity to specific cell types when therapeutic gene sequences (e.g., cytotoxic sequences, such as herpes simplex virus thymidine kinase) are delivered. FGF retargeted vectors are thus able to transduce cells which are normally insensitive to adenovirus infection.

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 26 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1998:440580 CAPLUS
DN 129:225334
TI Enhanced in vivo gene delivery to human ovarian cancer xenografts utilizing a **tropism-modified adenovirus** vector
AU Rogers, Buck E.; Douglas, Joanne T.; Sosnowski, Barbara A.; Ying, Wenbin; Pierce, Glenn; Buchsbaum, Donald J.; Manna, Debbie Della; Baird, Andrew; Curiel, David T.
CS Department of Radiation Oncology, University of Alabama at Birmingham, San Diego, USA
SO Tumor Targeting (1998), 3(1), 25-31
CODEN: TUTAF9; ISSN: 1351-8488
PB Stockton Press
DT Journal
LA English
AB Recombinant adenovirus vectors are of great interest in the context of cancer gene therapy due to their ability to accomplish efficient in vivo gene transfer. Despite this, however, it should be possible to increase the efficiency of gene transfer by **modifying** the **tropism** of **adenovirus** vectors such that they will bind to receptors which are highly expressed on target cancer cells. To achieve this, the basic fibroblast growth factor (FGF2) was used as a **ligand** to redirect adenovirus vectors to FGF receptors prevalent on SKOV3.i.p.1 human ovarian cancer cells. The FGF2 was conjugated to an antibody fragment (Fab), which inhibits adenovirus infection, and the resulting Fab-FGF2 conjugate used to specifically redirect an adenovirus vector carrying the luciferase reporter gene (AdCMVLuc) to SKOV3.i.p.1 cells in vitro. This anal. demonstrated that Fab-FGF2 modified AdCMVLuc achieved a level of gene expression that was greater than when adenovirus alone was used. More importantly, the Fab-FGF2 conjugate was able to enhance significantly the in vivo expression of the luciferase gene in SKOV3.i.p.1 tumors implanted i.p. in nude mice. Thus, this work demonstrates that adenovirus vectors can be modified to enhance gene transfer in vivo. Future studies will det. if the efficacy of therapeutic adenovirus vectors can be enhanced using these modifications.

L25 ANSWER 27 OF 30 MEDLINE DUPLICATE 10
AN 1998133166 MEDLINE
DN 98133166 PubMed ID: 9472563
TI Use of a novel cross-linking method to **modify adenovirus tropism**.
AU Rogers B E; Douglas J T; Ahlem C; Buchsbaum D J; Frincke J; Curiel D T
CS Gene Therapy Program, University of Alabama at Birmingham 35294, USA.
NC RO1 HL-50255 (NHLBI)
SO GENE THERAPY, (1997 Dec) 4 (12) 1387-92.
Journal code: 9421525. ISSN: 0969-7128.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199803
ED Entered STN: 19980312
Last Updated on STN: 19980312
Entered Medline: 19980303
AB Recombinant adenovirus (Ad) vectors can accomplish efficient in vivo gene transfer and thus are important in the context of a variety of gene therapy approaches. The cellular receptor for the Ad fiber knob is prevalent on a number of normal tissues which undermines the targeting of Ad to specific tumor cells. Therefore, the ablation of native Ad tropism and the introduction of novel Ad tropism are both necessary to target Ad vectors specifically to tumors. In this study, we have developed a flexible method for cross-linking the Fab fragment of a neutralizing anti-knob monoclonal antibody (1D6.14) to a cell receptor **ligand** . The cross-linking moieties are complementary low molecular weight recognition units, similar in concept to the avidin-biotin system. For proof of concept, we cross-linked 1D6.14 Fab to the basic fibroblast growth factor (FGF2). The Fab and FGF2 conjugates were synthesized and characterized both structurally and functionally. The conjugates were then complexed with an adenovirus vector carrying firefly luciferase (AdCMVluc) and the resulting complex used to show infection of a number of tumor cell lines expressing FGF receptors. This cross-linking system should provide a rapid and convenient method of conjugating various **ligands** to the Fab fragment for targeting Ad vectors to different types of tumors.

L25 ANSWER 28 OF 30 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 97:548077 SCISEARCH
GA The Genuine Article (R) Number: XL048
TI Targeted adenoviral vectors for cancer gene therapy (Review)
AU Douglas J T; Curiel D T (Reprint)
CS UNIV ALABAMA, GENE THERAPY PROGRAM, 1824 6TH AVE S, WTI 620, BIRMINGHAM, AL 35294 (Reprint); UNIV ALABAMA, GENE THERAPY PROGRAM, BIRMINGHAM, AL 35294
CYA USA
SO INTERNATIONAL JOURNAL OF ONCOLOGY, (AUG 1997) Vol. 11, No. 2, pp. 341-348. Publisher: INT JOURNAL ONCOLOGY, C/O PROFESSOR D A SPANDIDOS, EDITORIAL OFFICE, 1, S MERKOURI ST, ATHENS 116 35, GREECE.
ISSN: 1019-6439.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 66
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB In order to realise the full potential of gene therapy as a rational approach to the treatment of cancer, it will be necessary to achieve delivery of the therapeutic gene selectively to target tumour cells. Such cancer cell-specific gene delivery is mandated in the context of locoregional or compartmentalised carcinomas, and is also an absolute requirement for the treatment of disseminated disease. Moreover, underlying any cancer gene therapy approach is the need to achieve a high level of efficiency of gene transfer to the target cells. Of the existing

viral and nonviral gene delivery vehicles, the adenoviral vector uniquely fulfils two requirements of an intravenously administered vector for cancer gene therapy: systemic stability and the ability to accomplish efficient transduction of cancer cells. However, it is necessary to **modify** native **adenoviral tropism** in order to achieve selective transduction of target tumour cells. A number of strategies have been developed for this purpose, involving genetic or immunological modifications to either of two adenoviral capsid proteins, the fibre and penton base. These strategies are designed to generate a targetable, injectable vector which would represent a major advance in the field of cancer gene therapy.

L25 ANSWER 29 OF 30 MEDLINE DUPLICATE 11
AN 97413199 MEDLINE
DN 97413199 PubMed ID: 9267842
TI Strategies to accomplish targeted gene delivery to muscle cells employing **tropism-modified adenoviral** vectors.
AU Douglas J T; Curiel D T
CS Gene Therapy Program, University of Alabama at Birmingham 35294-3300, USA.
NC R01 5025505
SO NEUROMUSCULAR DISORDERS, (1997 Jul) 7 (5) 284-98. Ref: 98
Journal code: 9111470. ISSN: 0960-8966.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971021
Last Updated on STN: 19971021
Entered Medline: 19971009
AB We are developing strategies to **modify** the **tropism** of **adenoviral** vectors to accomplish targeted transduction of muscle cells for DMD gene therapy. In one approach, we have introduced targeting **ligands** into the adenovirus fibre, which mediates the binding of the virus Ad5 to the primary cellular receptor. In order to incorporate these fibre-**ligand** fusions into recombinant adenoviral vectors, we have employed a method based upon homologous DNA recombination between a fibre-deleted, propagation-defective rescue plasmid and a shuttle plasmid encoding a variant fibre. To date, we have generated an adenoviral vector containing chimeric fibres composed of the tail and shaft domains of adenovirus serotype 5 and the knob domain of serotype 3. This modification altered the receptor recognition profile of the virus containing the fibre chimera. In an alternative approach to the generation of a targeted adenoviral vector, we conjugated folate to the neutralising Fab fragment of an anti-fibre monoclonal antibody. This Fab-folate conjugate was shown to redirect adenoviral infection of target cells via the folate receptor at a high efficiency. These studies suggest that it will be possible to achieve our goal of deriving targeted adenoviral vectors for muscle cell-specific gene delivery in vivo.

L25 ANSWER 30 OF 30 MEDLINE DUPLICATE 12
AN 1998298563 MEDLINE
DN 98298563 PubMed ID: 9634824
TI Targeted gene delivery by **tropism-modified adenoviral** vectors.
AU Douglas J T; Rogers B E; Rosenfeld M E; Michael S I; Feng M; Curiel D T
CS Gene Therapy Program, University of Alabama at Birmingham 35294, USA.
NC R01 5025505
SO NATURE BIOTECHNOLOGY, (1996 Nov) 14 (11) 1574-8.
Journal code: 9604648. ISSN: 1087-0156.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 199808
ED Entered STN: 19980828
Last Updated on STN: 19980828
Entered Medline: 19980814

AB The utility of adenoviral vectors for gene therapy is currently limited due, in part, to the widespread distribution of the cellular receptor for the adenovirus fiber that precludes the targeting of specific cell types. In order to develop a targeted adenovirus, it is therefore necessary both to ablate endogenous viral tropism and to introduce novel tropism. We hypothesized that these two goals could be achieved by employing a neutralizing anti-fiber antibody, or antibody fragment, chemically conjugated to a cell-specific **ligand**. To test this concept, we chose to target the folate receptor, which is overexpressed on the surface of a variety of malignant cells. Therefore, we conjugated folate to the neutralizing Fab fragment of an anti-fiber monoclonal antibody. This Fab-folate conjugate was complexed with an adenoviral vector carrying the luciferase reporter gene and was shown to redirect adenoviral infection of target cells via the folate receptor at a high efficiency. Furthermore, when complexed with an adenoviral vector carrying the gene for herpes simplex virus thymidine kinase, the Fab-folate conjugate mediated the specific killing of cells that overexpress the folate receptor. This work thus represents the first demonstration of the retargeting of a recombinant adenoviral vector via a non-adenoviral cellular receptor.